A Phase II Study of Nivolumab plus Ipilimumab in Patients with Recurrent/Metastatic Salivary Gland Cancers

PROTOCOL FACE PAGE FOR MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase II study evaluating the efficacy of nivolumab in combination with ipilimumab in patients with recurrent and/or metastatic (R/M) salivary gland cancers (SGCs). Patients will be enrolled to two cohorts: Cohort 1, patients with R/M adenoid cystic carcinoma ("ACC group"), and Cohort 2: patients with R/M SGC of any histology, except ACC ("non-ACC group"). Patients will be required to have RECIST v1.1 measurable disease, any number of prior therapies, and no previous exposure to immunotherapeutic approaches. For the ACC cohort, patients with non-salivary primary sites would be allowed.

The primary endpoint for the study is best overall response rate (BOR = CR+PR) documented by RECIST v1.1 criteria. Secondary endpoints are progression-free survival (PFS) and safety/tolerability of the drug combination. These endpoints will be evaluated in each cohort separately. An exploratory endpoint is to analyze tumor tissue and peripheral blood cell subsets for potential biologic correlates of immune activation and efficacy with combination therapy.

Enrolled patients will be treated with nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (1 cycle= 6 weeks). RECIST v1.1 response assessment will be at baseline and then approximately every 12 weeks (+/- 1 week) (or approximately every 2 cycles of combination treatment). Given the potential for delayed responses following short periods of disease progression, subjects may continue to receive therapy beyond radiographic progression in the absence of clinical deterioration and after discussion with the Principal Investigator. Patients will be continued on therapy until disease progression, unacceptable toxicity, patient withdrawal of consent, or investigator's discretion. Adverse events will be monitored from the start of therapy until 30 days after the last dose of drug.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives

To determine the best overall response rate (BOR) documented by RECIST v1.1 criteria of patients with recurrent/metastatic SGC treated with nivolumab and ipilimumab.

Secondary Objective

To determine the progression-free survival (PFS) of patients with recurrent/metastatic SGC treated with nivolumab and ipilimumab.

To determine the safety/tolerability of nivolumab and ipilimumab in patients with recurrent/metastatic SGC.

Exploratory Objectives

To identify in tumor tissue and peripheral blood cell subsets potential biologic correlates of efficacy with combination therapy.

3.0 BACKGROUND AND RATIONALE

Salivary gland cancers (SGCs): Salivary gland cancers (SGCs) make up 5% of all head and neck malignancies and less than 0.5% of cancers overall[1]. These tumors can arise either in major salivary glands (parotid, submandibular, or sublingual) or in minor salivary glands that are located throughout the upper aerodigestive tract. 80% of SGCs arise in the parotid gland, 15% in submandibular, and the remaining 5% in the sublingual gland or minor salivary glands. The current World Health Organization (WHO) classification for SGCs recognizes 24 different histologic subtypes[2]; the most common include adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma, adenocarcinoma, and salivary duct carcinoma (SDC). Recurrent and/or metastatic (R/M) SGCs are incurable diseases, commonly treated with cytotoxic chemotherapy with palliative intent, despite the lack of clinical trial evidence proving meaningful clinical benefit[3,4]. Indeed, there are no standard or FDA-approved treatments for R/M SGC, and only a modest amount of clinical trial data is available to guide chemotherapy selection. More prospective clinical research is needed to identify effective therapeutic options for these patients.

While diversity among SGC subtypes exists, ACC represents a particularly distinct entity. Clinical characteristics of ACC patients include a median age at diagnosis of 43, slight female predominance, almost equivalent incidence in major versus minor salivary glands, and a 5-year overall survival (OS; for all comers) of 70-90%[3]. Alternatively, SDC patients are characterized by a median age of 65, male predominance, a predilection for the parotid gland as the primary site, and a 5-year OS of 41%. These differences likely are rooted in the distinct genomic landscape of these tumors: ACCs are characterized by a relatively "quiet" genome (0.31 mutations/MB) and oncogenically driven by a unique t(6;9) translocation[5,6], while SDCs are characterized by a higher mutation rate (1.7 mutations/MB) and diverse oncogenic drivers[7]. These unique disease characteristics demand distinct clinical approaches. A significant subset of R/M ACCs initially take on an indolent course that allows for close surveillance before initiating therapy, while 1/3 may have much more aggressive disease resulting in mortality within 2 years of diagnosis. In contrast, R/M SDCs and other subtypes are more homogeneously aggressive, demanding immediate treatment. Indeed, previous SGC clinical trials were designed to evaluate therapies among ACC patients separately from other SGC histologies by defining two experimental cohorts: ACC and non-ACC trial arms[8,9]. This is a feasible study design that appropriately accounts for the starkest biologic and clinical distinctions noted among SGCs.

Combined T cell checkpoint blockade as a therapeutic strategy for R/M SGCs:
Immunotherapies directed at blocking inhibitory checkpoints to activate T cell immune responses is an effective therapeutic strategy for a variety of human cancers, but the utility of this approach for R/M SGC is not known. The programmed death protein 1 (PD-1)/PD ligand 1/2 (PD-L1/2) pathway is a well described immune checkpoint in which PD-L 1/2 expressed on the cell surface of antigen-presenting cells (APCs) or tumor cells engage PD-1 receptors on T cells to induce an inhibitory signal to block T cell activation. The expression of PD-1 ligands on tumors and in the microenvironment has been proposed to be a requisite adaptation by tumors to evade immune surveillance during oncogenesis and tumor

progression. The durable tumor regressions produced by agents that target this pathway in isolation provide the proof of principle that selective inhibition of T cell checkpoints can be an effective therapeutic strategy.

Recently, Mukaigawa et. al. reported that among a Japanese series of 219 surgically resected SGC tumors in the absence of metastatic disease, 22.8% expressed PD-L1 by immunohistochemistry (IHC), which was independently associated with poor disease-free survival[10]. The extent of PD-L1 positivity varied amongst tumor histologies, with expression most frequently detected in large cell carcinoma, SDC, adenocarcinoma NOS, carcinoma ex pleomorphic adenoma, and squamous cell carcinoma[10]. At the 2016 ASCO Annual Meeting, Cohen and colleagues presented the preliminary results for a cohort of PD-L1 positive, unresectable/metastatic SGC patients treated on a phase 1b trial with the PD-1 targeting antibody pembrolizumab (Merck; KEYNOTE-028)[11]. Among 26 evaluable patients, three partial responses (11.5%) and a 31% rate of tumor regression were observed. This preliminary data indicates that targeting PD-1 may have modest activity for a subset of SGC patients, and also suggests the hypothesis that combining PD-1 pathway blockade with other immune checkpoint inhibitors may further augment T-cell activation to enhance clinical efficacy.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is an activation-induced T-cell surface molecule that negatively regulates T-cell dependent immune responses. CTLA-4 engagement of the APC-expressed ligands CD80 (B7.1) and CD86 (B7.2) blocks the co-stimulatory CD28:B7 signal that T cells require for full activation (proliferation, cytokine secretion, and effector function). Relative to the PD-1 pathway, CTLA-4 is a non-redundant inhibitory T cell signal that when inhibited in combination can augment T cell activation/ tumor infiltration to enhance clinical activity[12,13]. Combined checkpoint blockade has now been clinically tested in several human malignancies with the most mature data developed for untreated advanced melanoma patients[14-17]. In a 945 patient phase III trial, the combination of the PD-1 targeting antibody nivolumab and the CTLA-4 targeting antibody ipilimumab produced superior progression-free survival and overall response rates (ORRs) compared with ipilimumab alone among untreated, unresectable melanoma patients[15]. Descriptively, the combination was also superior to nivolumab alone (the study was not statistically powered to evaluate this comparison). While nivolumab alone produced higher PFS (14 months vs. 5.3 months) and ORR (57.5% vs. 41.3%) in the PD-L1-positive group compared to the negative group, the nivolumab plus ipilimumab combination yielded similar PFS benefit in both groups (PFS, 14 months vs. 11.2 months) but a higher response rate in the PD-L1 positive group (ORR, 72.1% vs 54.8%). This combination is now FDA-approved for melanoma patients.

The significant efficacy observed with the nivolumab/ipilimumab combination irrespective of PD-L1 status is of particular interest given the variable extent to which PD-L1 expression has been observed amongst different SGC histologist. Preclinical data also suggests that beyond activating effector T cells, a critical mechanism by which CTLA-4 inhibition enhances anti-tumor immunity is by targeting regulatory T (Treg) cells, which express high levels of

CTLA-4[18]. Ipilimumab can be engaged by FcγRIIA, which facilitates Treg depletion via antibody-dependent cell-mediated cytotoxicity (ADCC) by monocytes[19]. Indeed, patients with malignant salivary gland tumors possess a higher percentage of Tregs, CTLA-4^{+}CD4^{+} T cells, and lower Th17/Treg ratio in the periphery compared with patients with benign salivary tumors as well as control subjects[20]. We propose the hypothesis that CTLA-4 inhibition with ipilimumab will augment the preliminary activity reported with PD-1 targeting in SGC patients by enhancing both effector T-cell function and depleting/inhibiting the Treg population, independent of PD-L1 expression status.

Nivolumab: Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets PD-1. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, RCC, and some lymphomas. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC and in subjects with unresectable or metastatic melanoma. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma[15,16].

The overall safety experience with nivolumab is based on approximately 8,600 subjects treated with either monotherapy or in combination with other therapeutics. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of adverse events (AEs) to nivolumab dose level. Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. In general, for monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with NSCLC, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade.

Ipilimumab: Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal antibody (mAb) that binds to CTLA-4 and blocks the interaction with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell (Treg) function, which may contribute to a general

increase in T-cell responsiveness, including the anti-tumor response. Yervo™ (ipilimumab) has been approved for use in over 47 countries including the United States (US, Mar-2011), the European Union (EU, Jul-2011), and Australia (Jul-2011).

Bristol-Myers Squibb (BMS) and Medarex, Inc. (MDX, acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing more than 19,500 subjects (total number of subjects enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, as well as a compassionate use program. The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies. Phase III programs are ongoing in melanoma, prostate cancer, and lung cancer. In melanoma, two completed Phase III studies (MDX010-20 and CA184024) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively.

The safety profile of ipilimumab is generally consistent across these trials with a) the majority adverse events (AEs) being inflammatory in nature, which is consistent with the proposed mechanism of action of ipilimumab; b) the same types of such immune-mediated events in the gastrointestinal (GI) tract, skin, liver, and endocrine system being reported; and c) most of these events being manageable with immune suppressive therapies.

Nivolumab in combination with ipilimumab: 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3-mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD. Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. The safety profile of nivolumab plus ipilimumab has been consistent with the mechanisms of action for each agent, though the frequency and severity of the AEs are increased with the combination. The majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in proposed management guidelines.

Both the efficacy and safety of the combination has been most extensively evaluated in melanoma patients, though preliminary data has also been generated in renal cell carcinoma, glioblastoma, and non-small cell lung cancer (NSCLC) patients. The following summarize the clinical experience to date with an emphasis on the safety and toxicity profile of the combination (taken from the *Investigator Brochure*).

Melanoma

In BMS trial CA209069 (“Phase 2 study of nivolumab in combination with ipilimumab vs. ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic

melanoma"), the combination of nivolumab with ipilimumab demonstrated clear evidence of clinical activity over ipilimumab monotherapy, as measured by statistically significant improvements in ORR and PFS, and a higher proportion of subjects with complete responses[16]. In BMS trial CA209067 ("Phase 3 study of nivolumab monotherapy or nivolumab in combination with ipilimumab vs. ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma"), the combination of nivolumab with ipilimumab demonstrated clear evidence of clinical activity over ipilimumab monotherapy, as measured by statistically significant improvements in ORR and PFS, and a higher proportion of subjects with complete responses[15]. Based on descriptive analyses, the combination of nivolumab with ipilimumab demonstrated improved PFS and ORR over nivolumab monotherapy.

Safety data for subjects with previously untreated unresectable or metastatic melanoma treated with nivolumab in combination with ipilimumab in CA209067 (313 subjects) and CA209069 (94 subjects) were pooled and safety analyses were performed for these pooled subjects receiving nivolumab in combination with ipilimumab (a total of 407 subjects). Based on the pooled analyses, nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg administered IV Q3W for 4 doses followed by nivolumab 3 mg/kg IV Q2W has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation. The following were the key safety findings for these pooled subjects:

- The most frequently reported drug-related AEs of any grade (≥ 15% of subjects) were diarrhea (43.0%), fatigue (35.4%), pruritus (33.4%), rash (31.0%), nausea (24.8%), pyrexia (18.7%), ALT increased (18.2%), AST increased (16.7%) and decreased appetite (16.2%). The most frequently reported drug-related Grade 3-4 AEs (≥ 5% of subjects) were colitis (9.6%), diarrhea (8.80%), ALT increased (8.4%), lipase increased (8.4%), and AST increased (5.9%).
- The majority of drug-related SAEs were Grade 3-4 in severity. The most frequently reported drug-related SAEs of any grade (≥ 2% of subjects) were colitis (11.1%), diarrhea (8.8%), pyrexia (3.7%), pneumonitis (2.7%), hypophysitis (2.2%), transaminases increased (2.2%), and adrenal insufficiency (2.0%). The majority of drug-related SAEs were Grade 3-4. The most frequently reported drug-related Grade 3-4 SAEs (≥ 2% of subjects) were colitis (8.8%), diarrhea (5.7%), and transaminases increased (2.2%).
- The majority of drug-related AEs leading to discontinuation of study drug were Grade 3-4 in severity. The most frequently reported drug-related AEs of any grade leading to discontinuation of study drug (≥ 2% of subjects) were colitis (10.1%), diarrhea (7.4%), ALT increased (4.7%), and AST increased (4.2%). These were also the most frequently reported drug-related Grade 3-4 SAEs leading to discontinuation of study drug (≥ 2% of subjects)
- The most frequently reported drug-related select AE categories with nivolumab + ipilimumab combination therapy were skin (61.9%), GI (46.4%), endocrine (29.7%), and hepatic (29.0%). The majority of select AEs were considered by the investigators to be related to study treatment.

- Drug-related select AEs were mostly Grade 1-2 in all categories with the exception of hepatic select AEs where the majority were Grade 3-4.
- Across categories, the majority of high-grade events subsequently resolved, including those for which immunosuppressive medication was not initiated.
- The majority of deaths (80/105) were due to disease progression. Study drug toxicity was considered responsible for 2 deaths; 1 subject died of ventricular arrhythmia within 30 days of the last dose and the other died of pneumonitis between 31 and 100 days of the last dose.
- Abnormalities in select hematology assessments and liver/kidney function tests were primarily Grade 1-2 in severity.
- The immunogenicity of nivolumab was low and not clinically meaningful.

Renal cell carcinoma

For renal cell carcinoma, the nivolumab plus ipilimumab has been evaluated in a phase I study (BMS trial CA209016). The most frequently reported drug-related AEs in subjects treated with 3 mg/kg nivolumab + 1 mg/kg ipilimumab from that study included fatigue (12 subjects, 57.1%), rash (8 subjects, 38.1%), diarrhea (6 subjects, 28.6%), and pruritus (6 subjects, 28.6%); the majority were Grade 1-2. The most frequently reported drug-related AEs in subjects treated with 1 mg/kg nivolumab + 3 mg/kg ipilimumab included fatigue (17 subjects, 73.9%); nausea (11 subjects, 47.8%), diarrhea, (10 subjects, 43.5%), ALT increased (9 subjects, 39.1%), AST increased (8 subjects, 34.8%), decreased appetite, lipase increased, and pruritus (7 subjects, 30.4% each). The majority were Grade 1-2.

Glioblastoma

For glioblastoma, a Phase 1 safety cohort found that the nivolumab in combination with ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg or nivolumab 3 mg/kg + ipilimumab 1 mg/kg) has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation. The following were the key safety findings for subjects treated in BMS trial CA209143:

- All subjects treated with nivolumab + ipilimumab experienced at least 1 drug-related AE. The most frequently reported drug-related AEs in subjects treated with nivolumab + ipilimumab included fatigue and diarrhea; the majority were Grade 1-2.
- In subjects receiving nivolumab 1 mg/kg + ipilimumab 3 mg/kg, the most frequently reported SAEs were ALT increased, colitis, diarrhea, and hypothyroidism (2 subjects, 20.0% each).
- Gastrointestinal (13/30), skin (12/30), and hepatic (10/30) were the most frequently reported select drug-related AE categories in subjects treated with nivolumab + ipilimumab. Skin was the most frequently reported select drug-related AE category in subjects treated with nivolumab monotherapy (4/10).
- The most frequently reported drug-related Grade 3-4 select AEs in subjects receiving nivolumab + ipilimumab included ALT increased (4/30), diarrhea, colitis, and AST increased (3/30 each). No drug-related Grade 3-4 select AEs were reported in subjects receiving nivolumab monotherapy.

- No drug-related deaths have been reported.

Rationale for the nivolumab 3 mg/kg every two weeks plus ipilimumab 1 mg/kg every 6 weeks dose/schedule: The FDA approved dose/schedule for unresectable or metastatic melanoma is nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every three weeks for 4 combined doses, followed by nivolumab 3 mg/kg every two weeks alone. CheckMate-012 was an open-label, phase I multicohort trial evaluating the safety and efficacy of nivolumab alone and in combination with a variety of agents, including nivolumab plus ipilimumab, for first-line treatment of Stage IIIB/IV non-small cell lung cancer (NSCLC) patients[21]. The nivolumab/ipilimumab regimens initially evaluated included the FDA approved schedule for melanoma as well as nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 combined doses, followed by nivolumab 3 mg/kg every two weeks alone. However, both of these schedules were deemed poorly tolerated with 25/49 patients (51%) developing Grade 3/4 treatment-related AEs, three treatment-related deaths, and a 33% discontinuation rate for Grade 3/4 treatment-related AEs. As a result, four additional cohorts were introduced to the trial for evaluation: nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 cycles, nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 12 weeks, and nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks. While each of these regimens were deemed to be better tolerated than the initial two schedules tested, the nivolumab 1 mg/kg dosing was associated with less clinical activity. Hence, only the safety and efficacy profiles observed with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 6 weeks or every 12 weeks were deemed promising for further clinical development. The nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks was evaluated in 39 patients. Among those 39 patients, 28 (72%) had AEs of any grade; 13 (33%) developed Grade 3/4 treatment-related AEs. Five (13%) patients discontinued therapy due to treatment-related AEs. No treatment-related deaths were observed as of February 28, 2016. Promising activity was also observed with this regimen as 15 (38%) patients developed partial responses. The nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 12 week cohort (n=38 patients) had comparable safety and a slightly higher rate of response (18 (47%) partial responses) to the ipilimumab every 6 week cohort. Notably, the study was not powered to formally compare safety or efficacy outcomes amongst the cohorts, and the slightly higher response rate in the ipilimumab every 12 week group may have been attributed to clinical imbalances within the small sample sizes treated in each cohort. Given the promising safety/efficacy profile and the hypothesis that greater ipilimumab exposure may be associated with greater clinical activity, the nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks was selected for evaluation in this phase II trial for R/M SGC population.

Study overview: The objective of this phase II clinical trial is to assess the efficacy and safety of nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks in two cohorts of SGC patients: Cohort 1, patients with progressive, R/M adenoid cystic carcinoma ("ACC group"), and Cohort 2: patients with R/M SGC of any histology, except ACC ("non-ACC group").

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase II study evaluating the efficacy of nivolumab in combination with ipilimumab in the treatment of patients with recurrent and/or metastatic (R/M) salivary gland cancers (SGCs). Patients will be enrolled to two cohorts: Cohort 1, patients with progressive, R/M adenoid cystic carcinoma ("ACC group"), and Cohort 2: patients with R/M SGC of any histology, except ACC ("non-ACC group"). Patients will be required to have RECIST v1.1 measureable disease, any number of prior therapies, and no previous exposure to immunotherapeutic approaches. For the ACC cohort, patients with non-salivary primary sites would be allowed, given that ACCs are biologically the same disease entity regardless of primary site.

The primary endpoint for the study is best overall response rate (BOR = CR+PR) documented by RECIST v1.1 criteria. Secondary endpoints are progression-free survival (PFS) and safety/tolerability of the drug combination. These endpoints will be evaluated in each cohort separately. An exploratory endpoint is to analyze tumor tissue and peripheral blood cell subsets for potential biologic correlates of immune activation and efficacy with combination therapy.

4.2 Intervention

Enrolled patients will be treated with nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (1 cycle= 6 weeks). Radiographic imaging and clinical assessments for RECIST v1.1 response assessment will be performed at baseline and then approximately every 12 weeks (+/- 1 week)(or approximately every 2 cycles). Given the potential for delayed responses following short periods of disease progression, subjects may continue to receive therapy beyond radiographic progression in the absence of clinical deterioration and after discussion with the Principal Investigator. Patients will be continued on therapy until disease progression, unacceptable toxicity, patient withdrawal of consent, or investigator's discretion. Adverse events will be monitored from the start of therapy until 30 days after the last dose of drug.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Table Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial	5-10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing

Table	Product Description				
Ipilimumab Solution for Injection	50 mg (5 mg/mL)	10 mL vial	6 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

*Nivolumab maybe labeled as BMS-936558-01 Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab and ipilimumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab or ipilimumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) and Ipilimumab Investigator Brochure section for "Recommended Storage and Use Conditions" and Appendix 1.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

NOTE: All eligibility criteria noted below are applicable for both **Cohort 1 (ACC patients)** and **Cohort 2 (non-ACC patients)** patients, unless specifically noted otherwise.

6.1 Subject Inclusion Criteria

- **Cohort 1 only:** Patients must have pathologically or cytologically confirmed adenoid cystic carcinoma. Cancers arising from non-salivary gland primary sites are allowed.
- **Cohort 2 only:** Patients must have pathologically or cytologically confirmed salivary gland cancer of any histology except for adenoid cystic carcinoma.
- Patients must have recurrent and/or metastatic disease not amenable to potentially curative surgery or radiotherapy.
- At least 2 weeks must have elapsed since the end of prior systemic treatment and/or 4 weeks since completion of radiotherapy with resolution of all treatment-related toxicity to NCI CTCAE Version 4.0 grade ≤1 (or tolerable grade 2) or back to baseline (except for alopecia, lymphopenia, or hypothyroidism) prior to starting study drug treatment. Any number of prior therapies for recurrent/metastatic salivary gland cancer are allowed.

  NOTE: Patients previously treated with hormonal therapies (e.g. drugs targeting the androgen receptor) may continue these drugs prior to trial enrollment and concomitantly with study therapy.
- Patients must have RECIST v1.1 measurable disease.
- **Cohort 1 and acinic cell carcinoma patients in Cohort 2 only:** Patients must have documentation of a new or progressive lesion on a radiologic imaging study performed within 6 months prior to study enrollment (progression of disease over any interval is

allowed) **and/or** new/worsening disease related symptoms within 6 months prior to study enrollment. Note: This assessment will be performed by the treating investigator. Evidence of progression by RECIST criteria is not required.

- Age ≥ 18 years.
- ECOG performance status 0 or 1 (or Karnofsky ≥70%).
- Patients must have tissue from the primary tumor or metastases available for correlative studies. Either a paraffin block or at least 20 unstained slides are acceptable (30 unstained slides would be ideal). (If less than twenty unstained slides are available and a paraffin bloc is not available, the patient may be able to participate at the discretion of the investigator.)
- Patients must agree to undergo two research biopsies of (a) malignant lesion(s). Tumor tissue obtained prior to study consent or treatment as part of standard of care can also be submitted in lieu of performance of the first pre-treatment biopsy, if the Principal Investigator deems it to be of sufficient quantity/quality/timeliness. Patients may be exempt from biopsy if 1) the investigator or person performing the biopsy judges that no tumor is accessible for biopsy, 2) the investigator or person performing the biopsy feels that the biopsy poses too great of a risk to the patient, or 3) the patient's platelet count is <100,000/mcl or he/she cannot be safely removed from anti-coagulation therapy (if the anti-coagulation therapy needs to be temporarily held for the biopsy procedure). If the only tumor accessible for biopsy is also the only lesion that can be used for RECIST v1.1 response evaluation, then the patient may be exempt from biopsy. If the investigator deems a second research biopsy to be high risk after a patient has completed the first research biopsy, the patient may be exempt from the second biopsy.
- Screening laboratory values must meet the following criteria:
  - WBC ≥ 2000/μL
  - Neutrophils ≥ 1500/μL
  - Platelets ≥ 100 $x10^3$/μL
  - Hemoglobin > 9.0 g/dL
  - AST/ALT ≤ 3 x ULN
  - Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
  - Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

- Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

  WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

  Women who are not of childbearing potential are not required to use contraception.

- Women of childbearing potential must have a negative serum or urine pregnancy test upon study entry.

- Men who are sexually active with women of child bearing potential must use adequate contraception upon study entry until 31 weeks after the last dose of study treatment. Men who are surgically sterile or azoospermic do not require contraception.

6.2 Subject Exclusion Criteria

- Symptomatic metastatic brain or leptomeningeal tumors (asymptomatic or treated metastatic brain or leptomeningeal tumors are allowed).

- Current or prior use of immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone equivalents) or other immunosuppressive medications within 2 weeks of study drug administration. NOTE: Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

- Active, known, or suspected autoimmune disease within the past 2 years. NOTE: Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger

- Patients should be excluded if they have had prior systemic treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

- Patients should be excluded if they have a known history of testing positive for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus antibody (HCV antibody) indicating

acute or chronic infection (those with treated hepatitis B or C infection and a negative viral load prior to study entry would be eligible).

- Patients should be excluded if they have a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- History of allergy to study drug components.
- History of severe hypersensitivity reaction to any monoclonal antibody.
- Women who are pregnant or breast-feeding.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. Patient recruitment most likely will occur in the medical oncology clinics of the Head and Neck Disease management team. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. Investigators will discuss the study and review/sign the informed consent documents with the patient.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review.

It is anticipated the study will recruit 2-3 patients/months.

8.0 PRETREATMENT EVALUATION

Within 30 days of starting treatment, the following tests need to be done:

- History and Physical Examination
- Vital signs (pulse, blood pressure), including weight
- Performance Status (ECOG or Karnofsky Performance Status)
- Radiology studies (CT or MRI) for disease assessment.

- Record of concomitant medications
- Signed Informed Consent Form
- Comprehensive Panel, including liver function tests (Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium)
- Complete Blood Count (including platelets)
- Thyroid stimulating hormone (TSH) level
- Serum or urine beta-hcg (pregnancy test) in women of child-bearing potential (within 14 days of receiving study drug).
- Request for archival tumor tissue (if tissue is not already available at MSKCC, receipt of tissue is not required for study enrollment or initiation.)
- Research blood draw (this can be performed any time prior to start of study drug): approximately 10 mL of blood, preferably in a lavender top tube (with EDTA).
- Research peripheral blood collection: Peripheral blood samples will be collected in 4 CPT tubes (BD, 8-ml capacity, total blood volume collected~32 ml for PBMC purification for flow cytometric analysis) and 1 PAXgene tube (BD order #762165 or equivalent) (for purification of RNA/DNA for TCR analysis). The Cycle 1, Week 1 sample should be obtained prior to drug administration, but not more than 3 days prior to the start of treatment.
- Research tumor biopsy: The first of two research biopsies will be performed any time prior to Week 1 Day 1. Tumor tissue obtained prior to study consent or treatment as part of standard of care can also be submitted in lieu of performance of the first pre-treatment biopsy, if the Principal Investigator deems it to be of sufficient quantity/quality/timeliness. Patients may be exempt from biopsy if 1) the investigator or person performing the biopsy judges that no tumor is accessible for biopsy, 2) the investigator or person performing the biopsy feels that the biopsy poses too great of a risk to the patient, or 3) the patient's platelet count is <100,000/mcl or he/she cannot be safely removed from anti-coagulation therapy (if the anti-coagulation therapy needs to be temporarily held for the biopsy procedure). Radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores preferred) are allowed as long as it is considered safe for the patient. If the only tumor accessible for biopsy is also the only lesion that can be used for RECIST v1.1 response evaluation, then the patient may be exempt from biopsy. If the investigator deems a second research biopsy to be high risk after a patient has completed the first research biopsy, the patient may also be exempt from the second biopsy.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Administration

Nivolumab and ipilimumab according to the following dose/schedule (1 cycle= 6 weeks):

Nivolumab: 3 mg/kg IV every 2 weeks

Ipilimumab: 1 mg/kg IV every 6 weeks

When study drugs (ipilimumab or nivolumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. It is recommended that nivolumab be administered first. The second infusion will always be ipilimumab, and will start approximately 30 minutes after completion of the nivolumab infusion. At the investigator's discretion patients can be treated with nivolumab alone after 4 cycles for safety concerns. Specifically, if the patient experiences low grade oxicities (grade 1 or 2) related to study treatment that do not mandate discontinuing or holding study drugs, but which the Investigator judges may worsen with further combination treatment, the Investigator may use his or her discretion to discontinue Ipilimumab after 4 cycles of treatment (not mandatory).

BMS-936558 (nivolumab) is to be administered as a 60 minute IV infusion. Ipilimumab should then be administered as a 90 minute infusion.

Ipilimumab and nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

The dosing calculations should be based on the body weight.

If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. If the subject's weight differs by 10% or less from the weight used to calculate the dose, the dose may be continued based on the previous calculation or re-calculated based on the patient's new weight per investigator discretion. All doses should be rounded as per institutional standard practice.

9.2 Concomitant Medications and Therapies

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator.

Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative (limited-field) radiation therapy is permitted, if all of the following criteria are met:
  - The lesion being considered for palliative radiation is not being used as (a) RECIST measureable target lesion(s) for disease assessment on this study.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that the therapy does not interfere with the study endpoints, in the opinion of the investigator.
- Bisphosphonates or denosumab.

- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are considered stable by the treating physician.

- Concurrent administration of study drug(s) with corticosteroid use to treat or prevent an immune related adverse event is allowed.

9.3 Schedule of Events (for ALL patients initiating treatment)

9.3.1 Patients will initiate treatment with nivolumab and ipilimumab on Week 1. This will occur in the outpatient setting. Required laboratory tests (detailed in **Section 10**) can be performed up to 7 days prior to initiation of treatment. It is unnecessary to repeat these laboratory tests if the screening assessments of the same tests were performed within 7 days prior to first dose of therapy. All other Week 1 evaluations (detailed in **Section 10**) may be performed up to 3 days prior to initiation of study treatment.

9.3.2 Evaluations during treatment will be performed according to the schedule detailed in **Section 10**.

9.3.3 Guidelines for dose reductions are provided in **Section 11**.

9.3.4 Tumor measurements with CT and/or MRI will be performed as outlined in **Section 10.**

9.3.5 Treatment may be discontinued at any time for progression of disease, unacceptable toxicity, patient withdrawal of consent, patient non-compliance, or investigator judgment.

9.3.6 Given the potential for delayed responses following short periods of disease progression, subjects may continue to receive therapy beyond radiographic progression in the absence of clinical deterioration and after discussion with the Principal Investigator.

9.4 Correlative Studies

Exploratory objective: To identify in tumor tissue and peripheral blood cell subsets potential biologic correlates of immune activation and efficacy with combination therapy.

Tumor Analysis

(in collaboration with Tim Chan's laboratory in the Human Oncology Pathogenesis Program at MSKCC)

Rationale: We hypothesize that interfering with the PD-1/PD-L1 and CTLA-4 axes with the nivolumab/ipilimumab combination can result in the loss of tolerance to immunogenic SGC antigens/neoantigens which may be identified through genomic analysis of the tumors. Other molecular/genetic correlates to benefit with immunotherapeutic approaches identified in other disease settings will also be explored, including PD-L1 expression, tumor mutation burden, and neoantigen load. To evaluate the potential correlation of these factors to

therapeutic efficacy, we will perform whole exome and transcriptome analysis in fresh research biopsies and/or archival tissues.
Approach: The research biopsy samples will be divided for fixation and flash freezing at the discretion of the Principle Investigator. These samples will be used to evaluate the genomic and transcriptomic landscape of the tumors. Archival tissues may also be used if of sufficient quantity and quality.

DNA and RNA will be extracted from frozen samples and/or paraffin tissue. The research peripheral blood sample collected on the study will be used as a control, matched normal sample (microdissection of normal tissue in the tumor samples may also be used for this purpose).

DNA will be submitted for next generation sequencing, possibly whole exome or whole genome sequencing. The specific assay that will be employed to analyze for genomic alterations will be dependent upon the technology available at the time of analysis and the amount of DNA extracted. Comparisons of DNA between tumor and normal tissue (from the research blood draw) will be performed as appropriate, thus generating germline sequence data. There is no intention to analyze the germline data beyond utilizing it as a normal control for the tumor tissue analysis, and generally germline data will not be communicated to the patient. This data will be used to quantitate mutation load and formulate a neoantigen score.

Extracted RNA will be analyzed with RNAseq technology, or alternative assays, depending on technical limitations/assay availability. Computational approaches will also enable analysis of baseline immune infiltrates present in the tumor, including that of CD4, CD8, and Tregs. PD-L1 transcript levels on tumor cells will also be quantified. RNA data will also be used to define a set of expressed neoepitopes and explore gene expression signatures that may correlate with response.

Frozen tissues from the research biopsy may be evaluated for relevant protein targets by Western blot or other proteomic assays that may be available at time of analysis.

Fixed archival and/or research biopsy tissues may also be evaluated by immunohistochemistry (IHC) to assess changes in tumor immune infiltrates and tumor/immune cell protein expression (e.g. PD-L1 status). For patients in whom sufficient fresh tissue can be collected in the research biopsies, the tumor immune cell infiltrate (or tumor infiltrating lymphocytes (“TILs”) may be extracted and characterized by cytometric techniques, including flow cytometry or mass cytometry (CyTOF). PD-L1 status will be evaluated by immunohistochemistry in MSK laboratories and/or BMS.

For patients in whom two serial research biopsies are obtained, evolution of the mutation, neoantigen, and gene expression landscape in pre- and post-treatment samples will be analyzed to gain insights into immunoediting that may occur and infer what epitopes may be critical for efficacy. The gene expression data (RNAseq or other) data can be analyzed to evaluate how immune cell tumoral infiltration and immunologic gene signatures may change with therapy.

Note regarding genomic and transcriptomic analysis: In the course of this research it is possible that some patients whose tumors are analyzed through investigational "next-generation" profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #
- Contact: ocrgapirb@mskcc.org

Peripheral Blood Analysis

(in collaboration with Tim Chan's laboratory in the Human Oncology Pathogenesis Program and the Immune Monitoring Core Facility at MSK)

Rationale: We hypothesize that the impact of disrupting the PD-1/PD-L1 and CTAL-4 axes with the nivolumab/ipilimumab combination upon peripheral blood immune populations will correlate to clinical efficacy of therapy in SGC patients.

Approach: At the time points indicated in **Section 10**, peripheral blood samples will be collected: 4 CPT tubes (BD, 8-ml capacity, total blood volume collected~32 ml for PBMC purification for flow cytometric analysis) and 1 PAXgene tube (BD order #762165 or equivalent) (for purification of RNA/DNA for TCR analysis). Changes to these methods may be adapted depending upon the most recent, generally accepted protocols. Flow cytometry will be used to evaluate changes in T cell subsets at different time points. Alternative approaches to this analysis may be pursued depending upon the availability of new technologies, platforms, or approaches. Specifically, assays investigating the immunogenicity of tumoral antigens in *ex vivo* assays utilizing these collected PBMCs may be of value and will be performed to identify potential neoantigens or self antigens that are critical for mediating therapeutic efficacy.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

All evaluations/tests and research collections may be performed up to 3 days prior to the patient being treated.

Cycle/Week of Therapy *(1 cycle= 6 weeks)*	Pre-Study[a]	Cycle 1 Week 1[l]	Cycle 1 Week 3	Cycle 1 Week 5	Cycle 2+[f] Week 1	Cycle 2+[f] Week 3	Cycle 2+[f] Week 5	Off Study[g]
Weeks on study	-	1	3	5	7	9	11	-
Nivolumab[b]		X	X	X	X	X	X	
Ipilimumab[b]		X			X			
Informed consent	X							
Concurrent meds	X	X[d]	X	X	X			X
Physical exam	X	X[d]	X	X	X			X
Vital signs (pulse, blood pressure)	X	X[d]	X	X	X			X
Weight	X	X[d]	X	X	X			X
Adverse event evaluation	X	X[d]	X	X	X			X
CBC w/diff, plts	X	X[e]	X	X	X	X	X	X
Comprehensive panel[c]	X	X[e]	X	X	X	X	X	X
TSH	X				X			X
Beta-HCG (serum or urine)	X[i]							
Request for archival tumor tissue	X							
Research blood draw	X							
Research tumor biopsies[k]	X[k]	X[k]						
Research peripheral blood collection[j]		X			X			X
Tumor measurements[h]	X	CT and/or MRI will be performed every 12 weeks (+/- 1 week) (or approximately every 2 cycles). Objective responses should be confirmed with a second assessment performed at least 4 weeks later.						

a: See Section 8.0 for the timing of these tests/evaluations prior to the start of therapy.
b: Study drugs will be administered at the following doses/schedules: nivolumab 3 mg/kg IV every 2 weeks and ipilimumab 1 mg/kg IV every 6 weeks. At the investigator's discretion patients can be treated with nivolumab alone after 4 cycles for safety concerns.
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
d: These Week 1 evaluations maybe performed within 3 days prior to the start of treatment.
e: These Week 1 laboratory tests may be done up to 7 days prior to starting treatment. It is unnecessary to repeat these laboratory tests if the screening assessments of the same tests were performed within 7 days prior to the first dose of therapy.
f: These columns reflect the schedule of assessments/treatment required for Cycle 2 and subsequent cycles in the weeks designated.
g: Off-study evaluation will be performed within 30 days of the patient's last dose of study drug (Exception: Patients for whom removal from the study followed a prolonged interval during which administration of study drugs was held for greater than 30 days, the off-study evaluation needs to be performed within 30 days of the patient's last physical assessment by investigator physician).
h: The treating physician may reschedule radiologyscans due to treatment delays at his or her discretion . If the patient has CT and/or MRI scans completed early for any reason (e.g. suspicion of disease progression), the next set of scans maybe ordered in 12 weeks (+/- 1 week) from that assessment. Please see Section 13.0 regarding the altered schedule of radiographic assessments required for patients being treated beyond initial evidence of tumor progression.
i. Serum or urine pregnancy test is required within 14 days of drug treatment for all women of child-bearing potential.
j: Peripheral blood samples will be collected in 4 CPT tubes (BD, 8-ml capacity, total blood volume collected~32 ml for PBMC purification for flow cytometric analysis) and 1 PAXgene tube (BD order #762165 or equivalent) (for purification of RNA/DNA for TCR analysis). The Cycle 1, Week 1 sam ple should be obtained prior to drug administration, but not beyond 3 days prior to the start of treatment. Subsequent samples will be obtained on Cycle 2/Week 1, Cycle 3/Week1, and then Off Study. If the collection of all 4 CPT tubes and 1 PAXgene tube are not feasible, this will not be considered a protocol deivation.
k. The first of two research biopsies will be performed anytime prior to Week 1 Day 1. Tumor tissue obtained prior to study consent or treatment as part of standard of care can also be submitted in lieu of performance of the first pre-treatment biopsy, if the Principal Investigator deems it to be of sufficient quantity/quality/timeliness. The second research biopsy will be performed prior to the administration of the second dose of ipilim umab. Exceptions regarding the timing of the second biopsycan be made at the Principal Investigator's discretion, and will not be considered a violation. Patients may be exempt from biopsyif 1) the

investigator or person performing the biopsyjudges that no tumor is accessible for biopsy, 2) the investigator or person performing the biopsyfeels that the biopsyposes too great of a risk to the patient, or 3) the patient's platelet count is <100,000/mcl or he/she cannot be safely removed from anti-coagulation therapy (if the anti-coagulation therapy needs to be temporarily held for the biopsyprocedure). Radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsymaterial (at least 3 cores preferred) are allowed as long as it is considered safe for the patient. If the only tumor accessible for biopsyis also the only lesion that can be used for RECIST v1.1 response evaluation, then the patient may be exempt from biopsy. If the investigator deems a second research biopsyto be high risk after a patient has completed the first research biopsy, the patient may also be exempt from the second biopsy.

l. If Cycle 1 Week 1 labs fall below screening requirements, the patient can start treatment at the discretion of the treatin g investigator if safety is not compromised.

11.0 TOXICITIES/SIDE EFFECTS

There will be no dose modifications permitted. Dose reductions or dose escalations are not permitted.

Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events (AEs) that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological (see Appendix 3; these are guidelines, not required interventions).

Early recognition and intervention are recommended according to the management algorithms; and in addition include ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab or ipilimumab related uveitis.

The recommendations are to follow the algorithms in the nivolumab investigator brochure for immune related events; while the ipilimumab investigator brochure contains similar algorithms, the algorithms in the nivolumab brochure have been aligned to accommodate combinations as well as nivolumab monotherapy. (see also Appendix 3; IB algorithms and Appendix 3 instructions are guidelines, not required interventions).

Therefore, the algorithms recommended for utilization are included here for reference. Additional details on the safety of nivolumab and ipilimumab, including results from clinical studies, are available in the IB.

Dose Delay Criteria

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories.

Dose delay criteria, treatment resumption criteria, drug discontinuation criteria, and management algorithims described in this section and Appendix 3 are applicable for drug-related adverse events (adverse events that are possibly, probably, or definitely related to nivolumab, ipilimumab, or both). All study drugs must be delayed until treatment can resume.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event with the exception of fatigue, medically managed hypothyroidism or hyperthyroidism, tolerable Grade 2 AEs (except for grade 2 uveitis discussed below), and Grade 2 laboratory abnormalities other than Grade 2 creatinine, AST, ALT, and/or total bilirubin abnormalities
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities.
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 or 4 lymphopenia or asymptomatic amylase or lipase abnormalities do not require a dose delay

- Grade ≥ 3 AST, ALT, total bilirubin will require dose discontinuation

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Criteria to Resume Treatment

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with Grade 2 AST, ALT, and/or total bilirubin abnormalities may resume treatment when laboratory values return to baseline and management with corticosteroids, if needed, is complete
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (below) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with the Principal Investigator.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

If the criteria to resume treatment is met, scheduling of subsequent will be determined by treating investigator and PI.

Continuing treatment with both ipilimumab and nivolumab is preferred. However, resumption of therapy with just one drug (either nivolumab or ipilimumab) may be considered if 1) the investigator makes the judgement that proceeding with only one drug is necessary to possibly avoid recurrence of an adverse event that would require further dose delay, and 2) it is discussed with the Principal Investigator.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

Discontinuation Criteria

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related

uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:

- Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - Grade $\geq$ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

*In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia $\leq$ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Principal Investigator
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing

Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE 4.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000

solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Please refer to Section 10 regarding the timing of tumor measurement assessments.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (uni dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with nivolumab and ipilimumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline and have received at least one dose of therapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the

beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the

appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**

CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the

first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Treatment beyond progression: Subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

13.0 CRITERIAFOR REMOVAL FROM STUDY

- Disease progression on treatment with nivolumab and ipilimumab.
- Patients may be removed from the study for protocol non-compliance.
- If at any time the patient develops unacceptable toxicity he/she will be removed from study.
- A patient can be removed from the trial if a dose delay of > 6 weeks occurs, unless the PI deems it appropriate to keep the patient on the trial as per protocol guidelines (see Section 11).
- Participants can be removed from the study at any time if the study doctor feels that it is in their best interest to do so.
- Patients may withdraw consent from the study at any time.

Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessment that continued protocol therapy could elicit future clinical benefit and the subject is tolerating study treatment.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

Followup imaging to evaluate for further progression will be performed 4-8 weeks after the initial scan demonstrating disease progression. Subsequent scans may be performed every 8 weeks (+/- 1 week) or every 12 weeks (+/- 1 week) per the investigator's discretion. Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm) and was not present during baseline scan. Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

14.0 BIOSTATISTICS

The primary endpoint of the study for each cohort is best overall response rate (BOR; CR+PR by RECIST v1.1). The ACC (Cohort 1) and non-ACC cohorts (Cohort 2) will be assessed separately. For ACC, our recent literature review of all systemic chemotherapy studies reported for R/M ACC patients from 1966 to 2009 revealed that these were generally small studies of variable, poor methodological quality from which definitive conclusions regarding the efficacy of chemotherapy are impossible to establish[3]. Objective responses with cytotoxic chemotherapy were infrequent, and in 10 studies evaluating different targeted agents (imatinib, gefitinib, cetuximab, lapatinib, bortezomib (excluding the VEGR targeted TKIs)) involving 157 ACC patients, only 2 objective responses were reported (in response to high dose imatinib). Notably, there is no data addressing potential efficacy of systemic therapy beyond the first line setting in R/M ACC[3]. The same concerns regarding trial design and modest activity with chemotherapy apply to non-ACC histologies as well[4]. There currently is no standard therapy for SGCs. Therefore, we will adopt a BOR of 5% as the null hypothesis and a BOR of 20% as desirable. A minimax two-stage design will be used for each cohort. In order to detect a difference between an unacceptable ORR of 5% and a desirable ORR of 20% with a one-sided type I error of 10% and power of 90%, at least 1 response needs to be observed among the first 18 patients enrolled in the first stage. If this is achieved, then the study will progress to the second stage in which an additional 14 patients will be accrued. In order to move to the second stage of the study, the patient response in the first stage must occur within 6 cycles (or 36 weeks (+/- 2 weeks)) of drug treatment. At the end of the trial, at least 4 responses need to be observed among a total of 32 patients of the cohort to be considered worthy of further investigation. Maximum number of patients treated in both cohorts combined would be 64 patients.

Given the length of the observation period for response, if the decision on whether to proceed to the second stage cannot be made after the first 18 patients have been enrolled, the study will not halt and patients will continue to be enrolled. In the worst case scenario, all 32 patients will have been enrolled before the decision on whether to proceed to the second

stage can be made. In this case the study becomes a single-stage design in effect, which has the same type-I error rate, power, and rejection criterion for the null hypothesis as the original minimax two-stage design.

Patients who receive at least one dose of either study medication (nivolumab or ipilimumab) will be included in the evaluation of the primary objective. Patients who are enrolled, but withdraw consent or are removed from the study prior to obtaining the first response assessment while on study treatment can be replaced, except for those who were taken off study for progression of disease or toxicity (in these specific incidences, patients will be classified as non-responders).

Secondary endpoints will include measuring progression-free survival (PFS) with recurrent/metastatic SGC treated with nivolumab and ipilimumab, and assessing the safety/tolerability of the regimen.

PFS will be estimated using Kaplan-Meier methodology, with time origin at the start of the treatment. Patients will be followed until progression of disease or death related to disease, whichever come first. Patients removed from the study for reasons unrelated to the disease (e.g. moving, accidental death) will be counted as censored. Patients who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression, and are subsequently removed from study within the next radiographic assessment for progression, will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

Safety will be assessed in terms of AEs, laboratory data and vital sign data, which will be collected for all patients. Appropriate summaries of these data will be presented. AEs will be listed individually per patient according to CTCAE version 4.0, and the number of patients experiencing each AE will be summarized. The safety population will comprise all patients who receive at least one dose of study treatment.

Due to the limited sample size, the analyses investigating the association between correlative markers and BOR will be exploratory. These exploratory analyses will be evaluated within each cohort separately. Categorical markers will be correlated with BOR by Fisher's exact tests. Continuous markers will be correlated with BOR by logistic regression. Immune activation that occurs concomitant with experimental therapy will be serially assessed in the PBMC analysis performed for each patient. Specifically, the changes in T cell subsets that occur with therapy will be analyzed and interpreted as potential indicators of immune activation induced by drug therapy. Proportions of T cell subsets will be calculated with 95% confidence intervals at each time point and plotted over time to reveal any trend. The baseline proportions of T cell subset and changes in these proportions from baseline to last time point will be correlated with the response status univariately.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Not applicable.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into the secure Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

Whole exome or genome sequencing data (if collected) will be deidentified; samples will be labelled with patient study IDs to preserve links to clinical data. The deidentified genomic data will be stored to a protected server that is specifically set aside for clinical trial data.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1.

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol is assessed for the level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority is already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Risks, Benefits, Toxicities/side effects

Potential risks to human subjects include drug related toxicity, placement of IV catheters, phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan, PET scan). All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests.

If an adverse medical event occurs, the patient will first contact the primary oncologist or the Principal Investigator. At nights and on weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded.

Alternatives/options

Participation in this trial is voluntary. Depending on the specific details of the situation, patient options without being in a study might include:

• Other palliative chemotherapy off study.

• Participation in a different clinical trial

• Best supportive care

Financial Costs/Burdens

The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (third party insurer) will include hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG, and doctor's fees. Patients will not be charged the cost of analysis for the research correlates. The patient also will not be charged for the subsequent research analysis of these specimens. Nivolumab and ipilimumab is provided by BMS and therefore is not billable to research participants.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

It is also stated in the consent and Research Authorization that research data (e.g. genomic sequence) may be placed into databases monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government. It is difficult to identify genotype/phenotype specifics since multiple diseases are studied under the auspices of this protocol and therefore, the requirements for submission of genotype/phenotype data into the NIH GWAS Repository (or any other public database) will be followed as per the MSKCC IRB GWAS SOP-503.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The data the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to treatment(s)
- If the AE was expected
- Detailed text that includes the following
  - An explanation of how the AE was handled
  - A description of the participant's condition
  - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1 SAE Reporting to BMS

See Appendix 2 for Mandatory Adverse Event reporting information to be included in Investigator Sponsored Research protocols.

All Serious Adverse Events must be reported to BMS Worldwide Safety.

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study. This reconciliation will occur at least quarterly and be initiated by the sponsor/investigator. Sponsor/investigator will request a reconciliation report from: aepbusinessprocess@bms.com. During reconciliation, any events found to not be reported previously to BMS must be sent to Worldwide.Safety@BMS.com.

BMS SAE forms should be used, or if performed under a US IND a Medwatch or CIOMS form can be used as required by regulatory authorities..

Site specific forms will be requested for review.

The sponsor/investigator will be required to reconcile SAEs reported in the clinical database with SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E); worldwide.safety@bms. BMS requests this to be done quarterly and prior to the database lock or final data summary.

A summary of the process for the sponsor/investigator:

- Sponsor/Investigator sends a request to BMS GPV&E for a "*GPV&E reconciliation report"*. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The request should provide the BMS protocol ID, study title and PI, and sponsor/investigator protocol ID.
- BMS will send a report back to the sponsor/investigator. The data elements listed on the GPV&E reconciliation report will contain information the investigator can use for individual case identification. Cases on the list from BMS GPV&E should be compared to the SAE cases in the clinical database.
- If the sponsor/investigator determines a SAE case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Appendix 1: Sample of Drug Ordering and Pharmacy Reference Material

Appendix 2: Adverse Event Reporting

Appendix 3: Management Algorithms

APPENDIX 1 SAMPLE OF DRUG ORDERING AND PHARMACY REFERENCE MATERIAL

Initial Orders

- *Following submission and approval of the required regulatory documents, a supply of nivolumab and ipilimumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial.*
- *The initial order should be limited to the amount needed for two doses. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug products will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.*
- *Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing*

Re-Supply

- *Drug re-supply request form should be submitted electronically at least 7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.*
- *When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.*

Drug Excursions

- *Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form*

Please refer to the most recent version of the nivolumab and ipilimumab Investigator Brochure for additional information to be included as per institutional or regulatory standards.

Nivolumab (BMS-936558) Pharmacy Reference Material

As this is provided for guidance only, please see investigator brochure for additional information regarding preparation and administration.

Nivolumab has a concentration of 10 mg/mL and is provided in a 10 mL vial. Ten or five vials are provided in a carton.

Storage Conditions & Handling:

- Store at 2-8°C (36-46°F), protect from light, freezing, and shaking.

- If any temperature excursions are encountered during storage, please report these to BMS for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.
- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

  After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs. For further information, please either discuss with your BMS CSR&O protocol manager or refer to your site IP Destruction policies and procedures

  Use Time/Stability: Please refer to the appropriate section of the current Investigator Brochure or Addendum. Due to parameters surrounding the use time of nivolumab and ipilimumab, the time of preparation should be noted in the Pharmacy Source documents [accountability logs] or in study files as required for investigator sponsored research [FDA and GCP].

  The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2°-°-8°C (, 36°-46°F) and used within 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of BMS-936558-01 injection in the IV bag includes the product administration period.

  Preparation and Administration:

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles. *Note: Mix by gently inverting several times. Do not shake.*
2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV. bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection
3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*
4. ***Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL [IBV13 Addendum Section 3.2.2].***
5. *Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.*
6. Attach the IV bag containing the nivolumab solution to the infusion set and filter.

7. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

Ipilimumab Pharmacy Reference Material

Ipilimumab vials (10 mL) are shipped in quantities of four.

Ipilimumab (BMS-734016) Injection (5 mg/ml) must be stored refrigerated (2-8°C, 36-46°F) with protection from light and from freezing. Ipilimumab may be stored in IV infusion bags (PVC, non-PVC/non-DEHP) or glass infusion containers for up to 24 hours at room temperature (20-25°C, 68-77°F) or refrigerated (2-8°C, 36-46°F). This would include any time in transit and the total time for infusion. Drug must be completely delivered within 24 hours of preparation.

Storage Conditions & Handling:

Ipilimumab injection may be stored undiluted, 200 mg/vial (5 mg/mL), or following dilution to concentrations between 1 mg/mL and 4 mg/mL in 0.9% Sodium Chloride Injection (USP), or 5% Dextrose Injection (USP) in PVC, non-PVC/ or glass containers for up to 24 hours in the refrigerator (2°C to 8°C) or at room temperature/room light. For longer storage, ipilimumab should be kept refrigerated (2°C to 8°C) with protection from light.

Ipilimumab injection must not be frozen.

Partially used vials or empty vials of Ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

Preparation and Administration

As this is provided for guidance only, please see investigator brochure for additional information regarding preparation and administration.

1. As ipilimumab is stored long term at refrigerated temperatures (2-8ºC) and protected from light, allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.
2. Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.
3. Aseptically transfer the required volume of ipilimumab solution into a syringe. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses].
4. Do not draw into each vial more than once. Discard partially used vials or empty vials.
5. Ipilimumab solution should be added to an appropriate size infusion container to accommodate the calculated final volume.

   Total dose should be calculated using the most recent subject weight; if weight on dosing day differs by 10% from prior weight used to calculate dosing, the dose should be recalculated and study drug adjusted accordingly.

   Mix by GENTLY inverting several times. DO NOT shake.

Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

6. Visually inspect the final solution. If the initial diluted solution or final solution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.
7. Immediately after the infusion is complete, flush with an adequate amount of 0.9% Sodium Chloride injection (USP) or 5% Dextrose injection (USP) to completely flush the residual fluid (dead space) in your administration set (approximately 30-50mL); this will ensure that all active drug is delivered to the study participant
8. Safely discard any unused portion of the infusion solution. Do not store for reuse.

Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents. Ipilimumab is administered as an IV infusion only

APPENDIX 2 ADVERSE EVENT REPORTING

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety.
- If the BMS safety address is not included in the protocol document (e.g. multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (i.e. CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).
    - Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
    - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
    - In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.

- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

A ***nonserious adverse event*** is an AE not classified as serious.

Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE

- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

APPENDIX 3: MANAGEMENT ALGORITHMS

- These general guidelines constitute guidance (adherence is not required) to the Investigator. The guidance applies to all immuno-oncology (I-O) agents and regimens.
- A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.
- Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
- Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.
- The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used

Investigators should refer to the most current version of the nivolumab or ipilimumab IB for current recommendations for management of a specific Adverse Event of interest.

Information must be included in the protocol. The format should be that which is acceptable per institutional practices or procedures:

1. As an appendix to a protocol document [may necessitate a change/amendment to the protocol as information is updated]
2. As reference to the current version of the reference IB in the protocol or
3. As text in the protocol.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

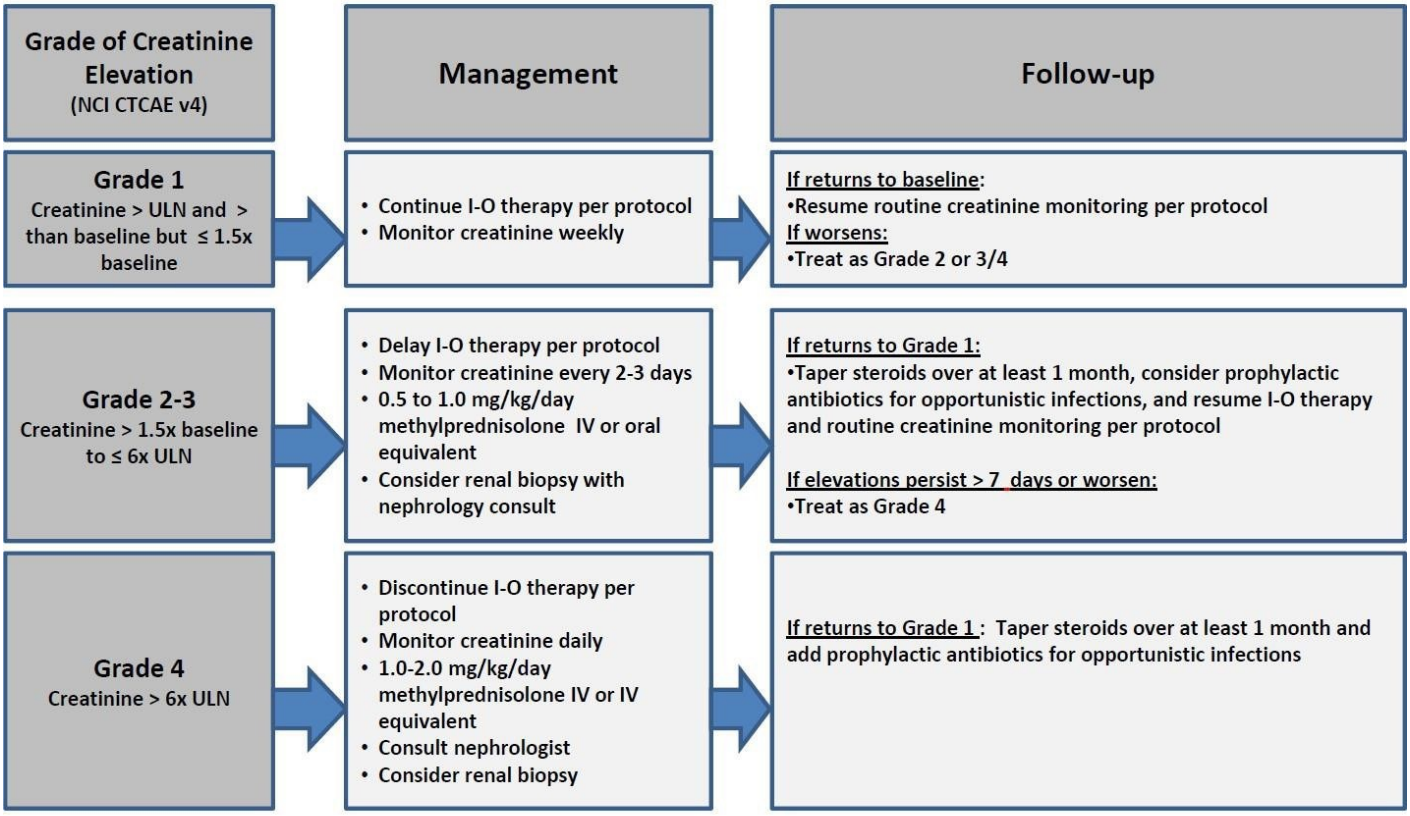
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

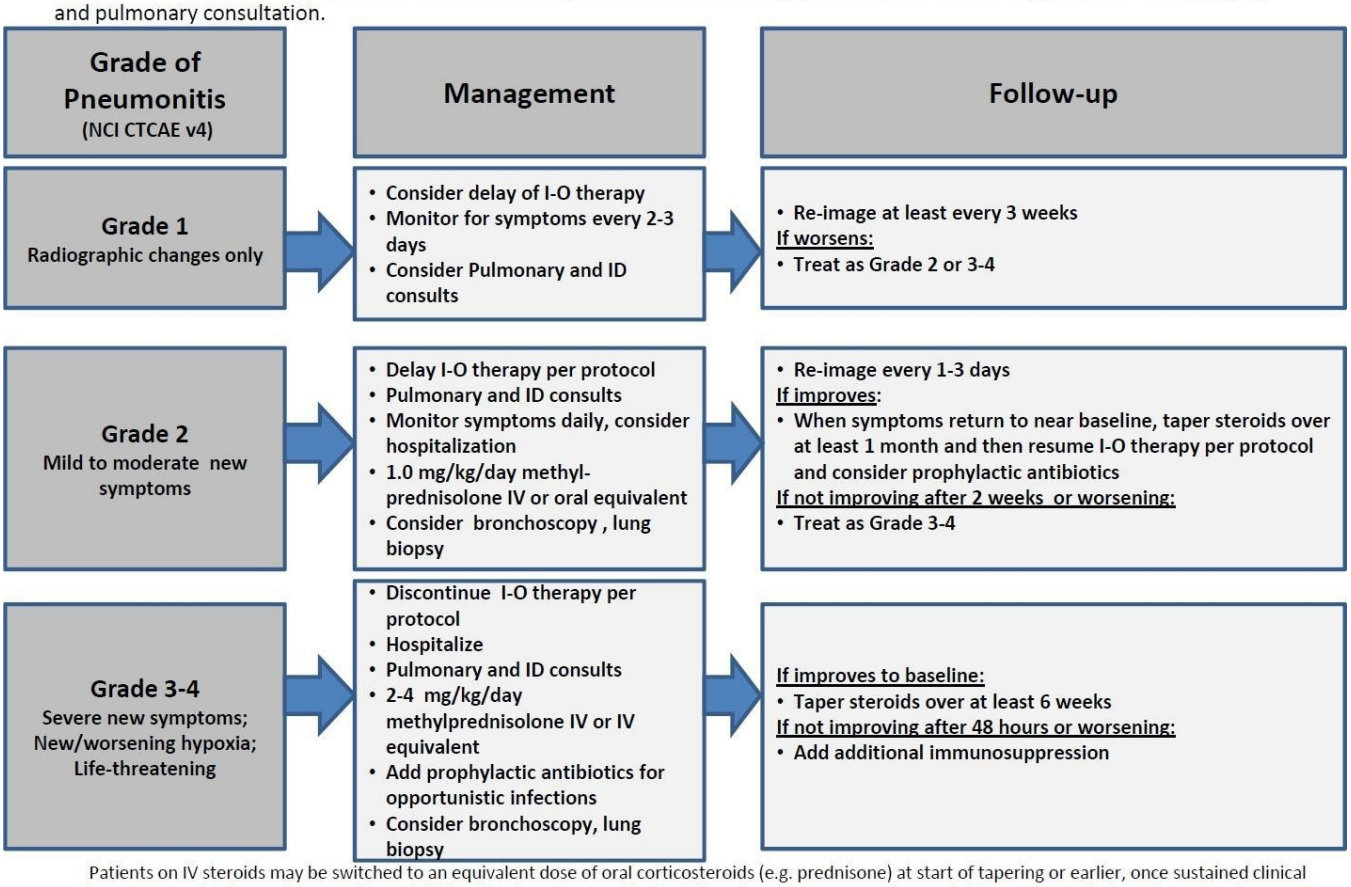


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

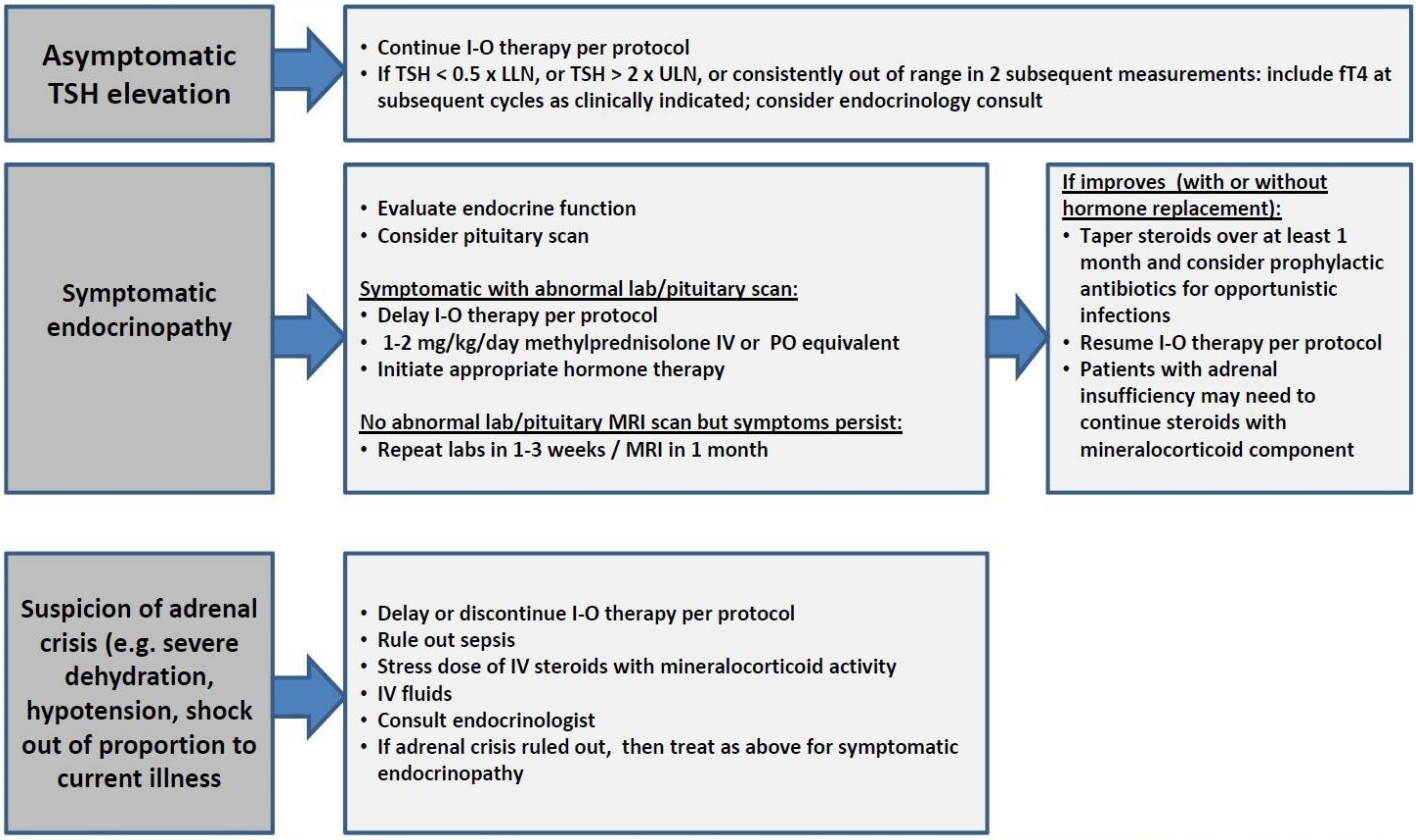
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

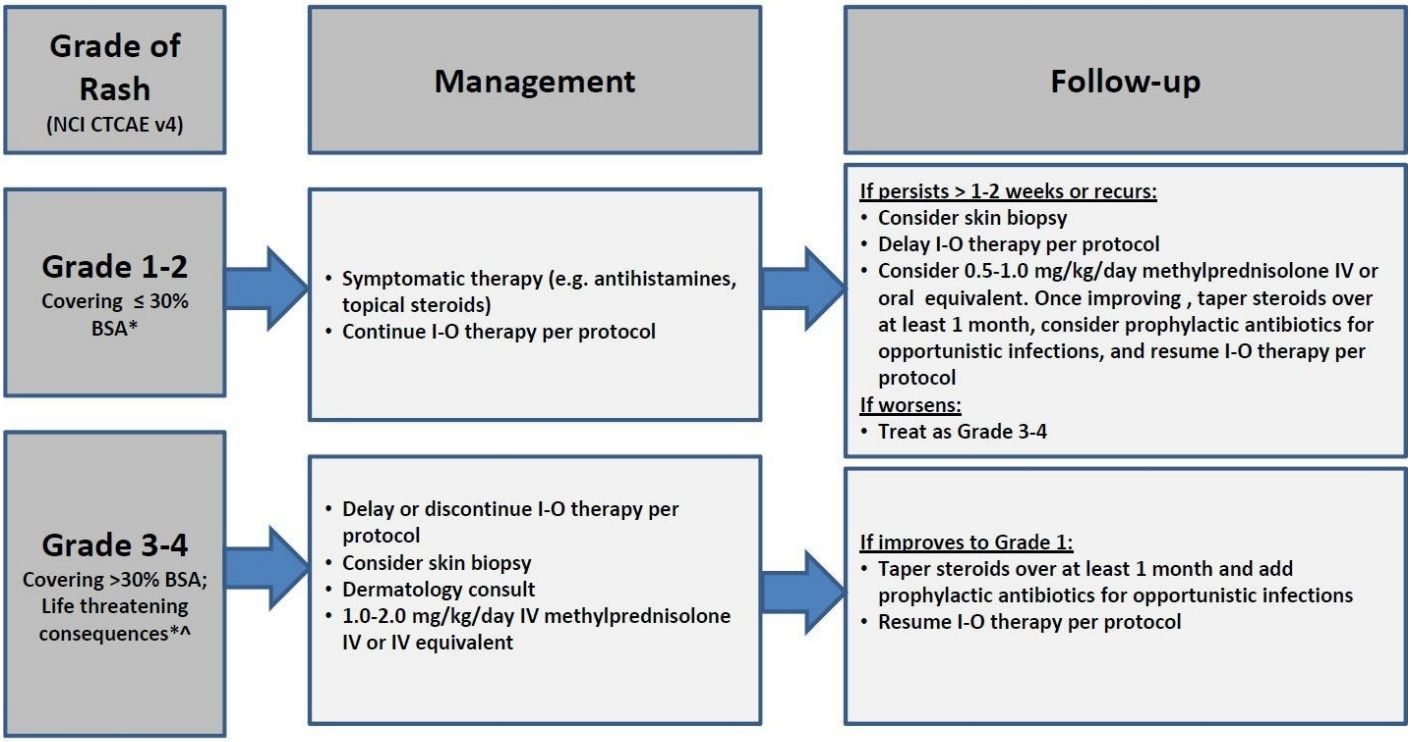


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016